Mechanism of cardiac damage: Ischemia-reperfusion injury

Eurasian Clinical and Analytical Medicine Review

Ischemia-reperfusion

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Abstract

If the blood flow slows down and the tissues and organs cannot be delivered the oxygen they need, the lack of sufficient oxygen level is called ischemia, and the restoration of blood flow to tissues and organs is called reperfusion. The damage that occurs after ischemia-reperfusion is called ischemia-reperfusion injury. The complexity of the mechanisms that cause ischemia-reperfusion injury prevents the complete elucidation of this mechanism. Ischemic conditions may lead to irreversible consequences such as cerebral infarction and myocardial infarction. Myocardial ischemia-reperfusion injury is a pathogenic mechanism of heart failure and myocardial infarction and is a major health problem worldwide. Several important pathological processes are involved in ischemia-reperfusion injury, including oxidative stress, programmed cell death (ferroptosis, apoptosis, necrosis), fibrosis, cardiomyocyte hypertrophy, and inflammatory response. Many studies have been conducted to clarify the mechanisms and treatment modalities involved in ischemia-reperfusion injury. This is because ischemia-reperfusion injury is one of the leading causes of death, similar to myocardial infarction, peripheral vascular diseases, etc. Recently, revascularization methods have been used to reduce the level of ischemic damage. In this review, we will briefly discuss the mechanism of cardiac injury and ischemia-reperfusion injury.

Keywords

ischemia-reperfusion injury, myocardial ischemia-reperfusion, cardiovascular injury

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Introduction

If the oxygen required by tissues and organs cannot be delivered with the slowing of blood flow, the lack of sufficient oxygen level is called ischemia, and the restoration of blood flow to tissues and organs is called reperfusion. The damage that occurs after ischemia-reperfusion is called ischemia-reperfusion injury (IRI).[1] The complexity of the mechanisms leading to IRH prevents a complete elucidation of this mechanism. Ischemic conditions may lead to irreversible consequences such as cerebral infarction and myocardial infarction (MI).[2] Myocardial IRH is a pathogenic mechanism of heart failure and myocardial infarction and is a major health problem worldwide.[3] Several important pathological processes such as oxidative stress, programmed cell death (ferroptosis, apoptosis, necrosis), fibrosis, cardiomyocyte hypertrophy, and inflammatory response are involved in IRH. Many studies have been conducted to clarify the mechanisms and treatment modalities involved in IRH.[2] Because IRH damage is among the causes of mortality similar to MI, peripheral vascular diseases, etc. [4] Recently, the level of ischemic damage has been tried to be reduced with the use of revascularization methods.[5] These methods include coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). However, since the targeted success against reperfusion injury has not been achieved, new techniques are needed. Even treatment with statins, ACE inhibitors, and beta blockers to prevent MI and poor left ventricular remodeling after revascularization.[6] fails to stop the triggering of the acute inflammatory response.[7]

The pathophysiology of IRH is not easily understood because the damage occurring in the ischemic phase and the damage occurring in the reperfusion phase cannot be distinguished exactly. Studies have revealed that there are four types of reperfusion injury;

1. Fatal reperfusion injury: Fatal reperfusion injury is defined as the death of cardiac myocytes that are viable before reperfusion after reperfusion.
2. Vascular reperfusion injury: This is damage caused by the absence of reflow (No-refl ow) and loss of coronary vasodilator supply.
3. Myocardial Stunning: A mechanical dysfunction associated with decreased energy synthesis, with alternating cycles
4. Reperfusion Arrhythmias: Ventricular tachycardia and fibrillation immediately after reperfusion.[8]

What are the risk factors in IRH?

Genetic factors, hereditary factors, gender, and advanced age are risk factors in IRH. However, there is not much that can be done to prevent their effects. Other important comorbidities, such as gender-specific folate deficiency, sedentary lifestyle, use of recreational drugs and tobacco products, excessive and chronic alcohol consumption, hyperhomocysteinemia and hyperlipidemia, hypertension, obesity, and metabolic syndrome can be reduced or controlled. However, conditions including diabetes mellitus, rheumatoid arthritis, acute stress, and depression are significantly associated with the incidence of myocardial infarction and cardiovascular disease in women.[9]

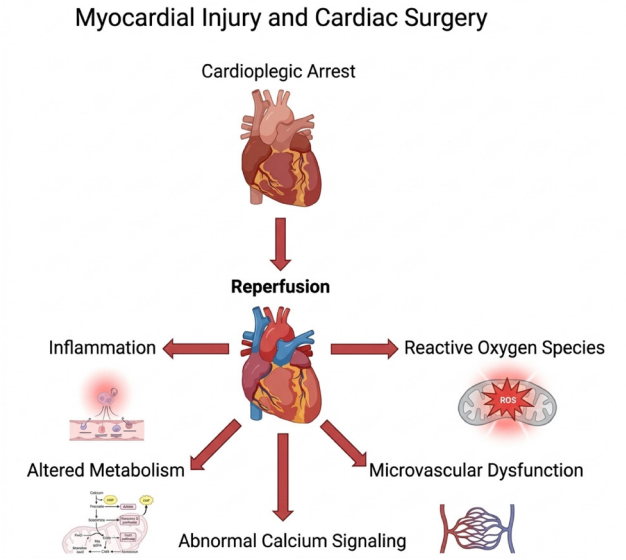

Figure 1. Mechanisms of myocardial damage in cardiac surgery and factors that increase this damage [12]

Inflammation and ischemia-reperfusion injury

During the ischemic state, intracellular ions such as calcium, sodium, and hydrogen increase, and tissue acidosis occurs. This results in adenosine triphosphate (ATP) depletion, structural damage to mitochondria, myofibrillar hypercontractility, and myocardial stunning. Cardiac myocytes have a high density of mitochondria. This is because myocytes have a high energy requirement. Proapoptotic stimuli and reactive oxygen species (ROS) are synthesized in mitochondria during the triggering and development of IRH. In addition, the inflammatory response is mediated by cardiac macrophages and leukocytes that can easily migrate from the damaged vascular endothelium to the interstitial space.[7] As occurs in normal cell death, damage-associated molecular patterns (DAMPs) are also transferred into the environment that activates immune cells such as leukocytes. Proinflammatory cytokines are secreted by leukocytes, which exacerbate ischemic damage. For example, studies have shown increased levels of tumor necrosis factor-alpha (TNF-α) in the infarcted area after MI, in a study conducted on mice with reduced TNF-α receptors, it was revealed that there was a shrinkage in the infarct area and resistance to IRH compared to the control group.[10] Interleukins 1 and 6 (IL-1 and IL-6) have also been described to increase ischemic damage.[11] Therefore, reperfusion occurring immediately after ischemia involves mechanisms that trigger the formation of damage in the heart (Figure 1).[12]

Hypothermia and cardioplegia applications are among the methods used to alleviate the damage caused by cardiac ischemia and IRH in cardiac operations. Myocardial oxygen demand has been proven to decrease significantly with the use of cardioplegic solutions. [13] Reduction in myocardial oxygen demand means preservation of ATP stores and reduction of damage caused by metabolic disorders. [14]

Ischemic conditioning in cardiac surgery takes three forms;

1. Subjecting the myocardium to periods of ischemia before injury in order to reduce ischemic damage (ischemic preconditioning): application of the cardiac surgery method. That is, possible damage during surgery, including the use of cross-clamping to stop cardiac function.
2. Exposing the myocardium to ischemia as a result of an ischemic procedure (ischemic postconditioning),
3. IRH of a non-cardiac vascular area (remote ischemic conditioning): in studies, it is generally induced by repeating several times a period of cuff inflation and relaxation in the right upper extremity to initiate ischemia/reperfusion of the peripheral muscle bed.[12]

Discussion

Since IRH in most organs occurs in the absence of microorganisms, the activated inflammatory response has been described as sterile inflammation. In addition, inflammatory responses to IRH are similar to those induced by pathogens. In both types of inflammatory responses, damage occurs simultaneously with the recruitment of leukocytes and neutrophils to the affected tissue area and the synthesis of chemokines, cytokines, and other proinflammatory stimuli.[15] In examinations performed on the heart, it was found that leukocytes were present in a large portion of capillaries with no-reflow after reperfusion. IRH has

been proven to be associated with the development of no-reflow, which is characterized by a decrease in the number of perfused capillaries as a result of insufficient perfusion.[16] Gurusamy et al. explained that the increased microvascular permeability associated with neutrophils, triggered by IRH, is responsible for the failure of reflux in some tissues such as skeletal muscle after ischemia.[17]

Subjecting a non-cardiac vascular territory to IRH is referred to as remote ischemic conditionin.[12] In a randomized trial of patients undergoing elective CABG, CABG was associated with attenuated postoperative ischemic biomarkers, reduced all-cause mortality at one year, and reduced adverse cardiac events at one year. Another study involving valve surgery also reported an association between attenuated postoperative ischemic biomarkers and improved cardiac biomarkers, in part due to remote conditioning.[18]

Some signaling pathways that function in early heart development and are not active under normal conditions (Wnt signaling pathway) have been found to be critical in cardiovascular diseases.[19] These signaling pathways (Wnt signaling pathway) have been reported to be linked to many aspects of myocardial IRH, including programmed cell death,[20] oxidative stress, inflammatory response, fibrosis, and cardiac hypertrophy.[21] Other studies following these studies focused on how ischemic preconditioning can reduce ischemic damage in cardiac surgery. Studies on this topic have reported that ischemic damage, measured by a decrease in serum CKMB or troponin levels, is attenuated by preconditioning.[22]

Exposure of the myocardium to ischemia as a result of an ischemic procedure is called ischemic postconditioning.[12] In 51 patients who underwent CABG by Safaei et al., ischemic postconditioning immediately after surgical revascularization was triggered by three 60-second periods of ischemia followed by intermittent compression and relaxation of coronary grafts and reperfusion. Patients were divided into three groups. One group underwent ischemic postconditioning and the other two groups underwent pressure-controlled reperfusion from the aortic root only or reperfusion with postconditioning technique. Patients in the ischemic postconditioning group showed a reduction in the need for inotropes, improvement in ejection fraction, and postoperative rhythm disturbances after surgery.[22]

Limitation

The pathophysiology of IRH is not easily understood because the damage that occurs during the ischemic phase is not well differentiated from the damage that occurs during the reperfusion phase. It is very difficult for clinicians to determine a treatment method that they can use to ameliorate the damage. Therefore, more extensive studies are needed to investigate ischemic disorders, especially myocardial IRH, in more detail.

Conclusion

IRH is the leading cause of death in ischemic disorders.[8] As the underlying mechanism of myocardial IRH is complex, complex multi-targeted therapy may be effective in ameliorating reperfusion injury. Therefore, new therapeutic targets should be explored to maximize the benefits of revascularization.[23]

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

Data Availability

The data supporting the findings of this article are available from the corresponding author upon reasonable request, due to privacy and ethical restrictions. The corresponding author has committed to share the de-identified data with qualified researchers after confirmation of the necessary ethical or institutional approvals. Requests for data access should be directed to bmp.eqco@gmail.com

Conflict of Interest

The authors declare that there is no conflict of interest.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

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